

(b) a plurality of molecules of interest, wherein each molecule of interest comprises [a] an oligonucleotide moiety that binds to a [specific or] complementary affinity anchor molecule oligonucleotide and a binding entity selected from the group consisting of [oligonucleotides,] peptides, antibodies, and combinations thereof.

Kindly cancel claim 14.

17. (Amended) A process for producing an array of molecules of interest localized to known locations, comprising:

(a) electrochemically synthesizing a plurality of different affinity anchor molecules at known locations within a porous matrix on an electrode [a] microarray device, wherein the affinity anchor molecule is an [selected from the group consisting of] oligonucleotides [, peptides and mixed oligo-peptides];

(b) providing a plurality of molecules of interest, wherein each molecule of interest comprises [a] an oligonucleotide moiety that hybridizes [binds] to a [specific or] complementary affinity anchor molecule and a binding entity selected from the group consisting of [oligonucleotides,] peptides, antibodies, and combinations thereof;

(c) contacting the plurality of molecules of interest with the microarray device, whereby the molecules of interest localize to known locations by binding the affinity anchor molecule to the complementary oligonucleotide moiety of the molecule of interest; and

(d) washing the microarray device to remove unbound molecules of interest.

Kindly cancel claim 18.

REMARKS

Applicant respectfully requests reconsideration of the above-identified patent application in view of the foregoing amendment and following remarks. Applicant has provided the same amendments that were entered in Amendment B (paper 10) filed on 06 September 2002 with the following additional changes/amendments. Specifically, in claim 13 the wherein clause in element (a) has the porous matrix overlaying each electrode cell instead of the entire electrode array. Support for the entire wherein clause can be found, for example on page 5 lines 2-4 ("A microarray of electrodes is coated with a porous membrane.") where it should be noted that "membrane" and "porous matrix" are terms used interchangeably. ("First, the array is coated with a biocompatible porous membrane that allows molecules to flow freely between the bulk solvent and the electrode." Page 11 lines 25-26). In addition, claims 13 and 17 were further amended to remove "oligonucleotides" from the Markush group, as the previous amendment to include oligonucleotides as the affinity anchor molecule made the inclusion of oligonucleotide as a molecule of interest to be redundant. No new matter has been added. Other amendments to claims 13 and 17 were made to be consistent with the selection of oligonucleotides as the affinity

anchor molecule. No new matter has been added. Entry of the foregoing amendment is respectfully requested. Claims 13, 15-17 and 19-20 are pending.

35 U.S.C. §112 Second Paragraph Rejection (Final Office Action)

Claims 1-12 were rejected under 35 U.S.C. §112 second paragraph in view of several items a through h.

a. Claim 13 was considered indefinite “in failing to define the spatial arrangement of the required components of the device.” The Examiner is looking for the juxtaposition of the porous matrix, electrode cells and affinity anchor molecules. Applicant respectfully points out that claim 13 is directed to a “microarray device” and microarrays are known in the art. Recently issued U.S. Patent 6,444,111 (a divisional of Montgomery cited in the prior art rejection below), for example, describes how to make element (a) of claim 13 wherein the affinity anchor molecule is an oligonucleotide. Therefore, as provided in element (a) of claim 13, the porous matrix is overlaying the electrode array, composed of electrode cells, and the oligonucleotides (affinity anchor molecules) are located and bound to the porous matrix.

With regard to the notion of “moiety that binds to” a specific affinity anchor molecule, that has been amended to also be an oligonucleotide. Applicant respectfully submits that it is well known in the art that an oligonucleotide will bind to or hybridize to a complementary oligonucleotide such that the first oligonucleotide TCTCTCTCTC will hybridize to the oligonucleotide moiety AGAGAGAGAG but not to CCCCCCCCCC. Therefore, claim 13 requires merely a self assembly of different molecules of interest wherein each molecule of interest has an oligonucleotide moiety that hybridizes to the corresponding first oligonucleotide in the porous reaction layer. Therefore, the orientation of the claim device of claim 13 is provided.

b. The Examiner objected to the use of the term “specific of complementary affinity anchor molecule.” Claim 13 was amended such that the term is now “complementary affinity anchor molecule.” The term is clear to a person skilled in the art. Complementarity is well known for oligonucleotides and illustrated with the 10-mer sequences illustrated above. Oligonucleotides only hybridize to each other if their sequences are complementary.

c. The Examiner objected to the notion of combinations of members of a Markush group in claim 13. Claim 13 has been amended such that the binding moiety is an oligonucleotide.

d. In claim 17, the Examiner objects to step (a) of “electrochemically synthesizing” as not having support in the specification. The process for electrochemically synthesizing oligonucleotides onto porous reaction layers on electrode array devices is known in the art (Montgomery). The process of electrochemically synthesizing oligonucleotides (and other oligomers through an electrochemical deprotection process) is described in the specification beginning on page 11. Thus, although some elements use different terms for the same purpose in

the specification, the teachings are provided in the specification for the process step of electrochemical synthesis.

e. The Examiner objects to some inconsistent use of terminology in the specification as between porous membrane and porous matrix. The terms “matrix” and “membrane” are used interchangeably. It should be noted that the specification also seems to use the terms “layer material” and “substrate” interchangeably with “matrix” and “membrane.” Further, the Examiner is confused regarding descriptions of spotted arrays on page 6 lines 11-15 of the specification and *in situ* electrochemically synthesized arrays on page 6 lines 33-34. Microarrays containing oligonucleotides (element (a) of claim 13) can be made by various techniques. The paragraph on page 6 lines 11-26 describes immobilization techniques. The following paragraph, spanning pages 6-7, describes *in situ* electrochemical synthesis techniques and references (and incorporates by reference) Montgomery (cited in the prior art rejection below). The notion of diffusion within a solution (“allows molecules to flow freely between a bulk solvent and an electrode”) is quite different from the notion of a “porous membrane” as a “substrate.” The process of diffusion in a solution is part of the *in situ* electrochemical synthesis process described in Montgomery. The porous membrane/matrix is a substrate upon which the affinity anchor molecules (oligonucleotides) are synthesized.

f. The term “known locations” in claim 17 is a common term used in the field of microarrays. Generally microarrays have sites arranged in rows and columns. A know location is a particular row number and column number. Similarly, if one goes to a baseball stadium, the ticket will have a seat identifier by section, row and seat such that the ticket is for a known location.

g. The Examiner alleges for claim 17 that the specification is “directed to an array of electrodes” and claim 17 is not restricted to such an array of electrodes. Applicant has amended claim 17 to describe the microarray device as an electrode microarray device. Therefore, electrodes are present.

h. The Examiner alleged that claim 17 did not contain antecedent basis for “the complementary moiety of the molecule of interest.” Applicant has amended claim 17 so that the term now reads “the complementary oligonucleotide moiety of the molecule of interest” having antecedent basis in element (b).

In summary, all of the objections, a through h, have been addressed by the foregoing remarks and the foregoing amendment.

Advisory Action Item 3

In Item 3 of the Advisory Action, the Examiner still seems to require some kind of a spatial context to claim 13 with regard to the spatial context of the electrode array device and the

plurality of molecules of interest. That spatial context is already provided in claim 13. The Examiner is urged to look at Figure 2 where an image of a piece of an electrode array is shown, or specifically 9 electrode cells, each roughly square shaped. As provided in claim 13 and described in the specification, a porous matrix (membrane) coats the electrode array including each electrode cell. That porous matrix is present in Figure 2 but it is transparent in the image. That porous matrix is described as coating the electrode array in the specification on page 11 lines 25-26 and page 5 lines 2-4. Therefore, spatially claim 13 provides an electrode array composed of electrode cells as illustrated in Figure 2. The porous matrix coats the electrode cells. As provided in claim 13, both the affinity anchor molecules (now essentially oligonucleotides) and the molecules of interest are located within the porous matrix. As provided in claim 13 element (a), the affinity anchor oligonucleotides are located within the porous matrix. As provided in claim 13 element (b), the molecules of interest contain an oligonucleotide moiety that is complementary to one of the oligonucleotides that is the affinity anchor oligos. Therefore, the spatial of functional relationship are that the molecules of interest bind to the affinity anchor molecules through hybridization of complementary strands. All of this is located in the porous matrix because claim 13 specifies that is where the affinity anchor molecules are located.

In addition, Montgomery is cited as a reference and is incorporated by reference. Montgomery teaches how one can synthesize affinity anchor molecules within a porous matrix and synthesize different sequences of affinity anchor oligos at different electrode cells. Therefore, that part of the porous matrix located above the electrode is where the chemistry take place. The electrochemical reaction takes place within the porous matrix but it is not an "immobilization" as the Examiner asserts but a hybridization of the sequences of the affinity anchor oligo to the oligo moiety of the molecule of interest.

In summary, the present invention is well described to a person skilled in the art. Applicant urges the Examiner to call the undersigned attorney of record for further explanation or for website references that illustrate the actual electrode arrays having a porous matrix described herein.

Advisory Action Item 4

In the Advisory Action, item 4 appears to be an additional rejection of claim 13 under 35 U.S.C. §112 second paragraph. Specifically, the Examiner inquires how "the 'porous matrix overlays the electrode array device.'" The Examiner's question in item 4 of the Advisory Action can be answered by reading the sentence on page 11 lines 25-26 and page 5 lines 2-4. Those sentences talk about coating the electrode array with a porous membrane. If one looks at Figure2, each "electrode cell" is one of the square-shaped units (there are 9 electrode cells shown in Figure 2) of this image shown looking down or through the porous matrix (membrane). Therefore, claim 13 (as currently amended) is not confusing because one can coat a solid object with a matrix or

membrane simply by dipping the solid object (an electrode array is a solid object) in a slurry that dries on a surface. Therefore, claim 13, as amended in Amendment B and presently in Amendment C, is clear and describes the metes and bounds of the present invention with particularity.

35 U.S.C. §102/103 Rejections

Claims 13-20 were rejected under 35 U.S.C. §102 as anticipated by or under 35 U.S.C. §103 as unpatentable in the Final Office Action over each of Montgomery, Ackley et al., Heller et al. or Hafeman et al. The Examiner has alleged that the argument provided in Amendment A “is inconsistent with the actual descriptions of the references.” With regard to Montgomery, the Examiner pointed to column 5 lines 30-56 as a process “for the formation of oligomers by a process which binds one oligomer to another.” Applicant (Montgomery) respectfully disagrees with that characterization of Montgomery. The Examiner also characterized Ribí et al. as an “electrode array.” Applicant respectfully disagrees with that characterization of Ribí et al. The Examiner did not specifically discuss Ackley et al., Heller et al. or Hafeman et al. but there are passages provided in the first Office Action (dated 03 October 2001). Applicant respectfully traverses this rejection under both 35 U.S.C. §102 and 35 U.S.C. §103 because each of the references does not disclose (alone) or suggest (alone or in combination) the claimed invention of claimed microarray device of claims 13 and 15-16 or the process of claims 17 and 19-20. Applicant shall address this rejection on a cited reference-by-cited reference basis.

With regard to Montgomery, this reference and the passage cited by the Examiner refers to an *in situ* electrochemical synthesis process to synthesize oligomers, wherein oligomers include oligonucleotides. Montgomery is incorporated by reference within the specification of the present patent application (see page 6 lines 28-29 where the patent application serial numbers correspond to the later-issued Montgomery). The relevant parts of Montgomery¹ describe a microarray device having a plurality of oligonucleotides synthesized base-by-base by an electrochemistry process. Therefore, Montgomery does not teach the binding of one oligonucleotide to another (a process also known as hybridization) but of the electrochemical deprotection of a growing oligonucleotide to bind another based through standard phosphoramidite chemistry. Therefore, the Examiner’s assertion is incorrect. Montgomery describes a microarray device of claim 13 but only element (a). Montgomery does not describe or suggest element (b) of claim 13. Similarly, Montgomery describes the process of claim 17 step (a) but not steps (b) through (d).

no limiting
Lang

Applicant has amended claim 17 to only provide for **hybridization** of complementary **oligonucleotide** moieties. Therefore, the notion of binding of one nucleotide base to a growing

¹ It should be noted that the disclosure of Montgomery is broader than just an array of oligonucleotides but this is the most relevant comparison to the presently claimed invention.

oligonucleotide sequence in the Montgomery process for *in situ* electrochemical synthesis of oligonucleotide microarray device of claim 17 step (a) or claim 13 element (a) does not disclose or suggest all of the elements of claims 13 and 17, nor does it suggest the addition of the missing elements. Moreover, the amendment to claim 17 that oligonucleotides hybridize to each other (when of complementary sequences) is inconsistent with the Examiner's interpretation of anything that binds within the scope of the claims. Accordingly, Montgomery does not anticipate or render obvious the claimed invention.

With regard to Ribí et al., this reference does not even disclose an electrode array of claim 13 element (a). The cited sections (columns 6 and 7) in Ribí et al. only disclose standard biotin-avidin binding to each other, an indiscriminate binding and not the selective binding of only complementary oligonucleotide sequences as provided in the present invention. Moreover, the column 3 cited passage of Ribí et al. provides only "electrode arrays are provided, which are insulated from the sample medium while in electrical conducting relationship with the polymeric layer." However, the use of the words "electrode array" in Ribí et al. only refers to a single electrode and not a multiplexed plurality of electrodes in a microarray device. This dissimilar use of terminology is backed up by the fact that Ribí et al. relates to multilayered sensor devices that do not have the multiplex characteristics that the microarray devices have as in Montgomery. There is only, at most, one single electrode is provided in each "electrode array" as this term is used in Ribí et al. Support for different use of the notion of "array" in Ribí et al. is found in column 22 lines 38-46 where multiple arrays of ten electrode arrays (using Ribí terminology) "allows for ten independent measurements to be made simultaneously." Therefore, the electrode array of Ribí et al. is a single electrode device and not a multiplexed microarray device of the present invention and of Montgomery. Accordingly, Ribí et al. does not disclose, anticipate or suggest any of the elements of the presently claimed invention.

With regard to Ackley et al. (column 6 lines 3-41) this disclosure proves an electrode containing microarray device (similar to claim 13 element (a)) but made differently from the *in situ* electrochemistry process of Montgomery. Therefore, much like Montgomery, Ackley et al. does not disclose or suggest claim 13 element (b). Claim 13 element (b) provides a plurality of molecules of interest but each molecule of interest comprises an oligonucleotide moiety, that is a moiety or part of a molecule, not the entire molecule. Ackley et al. adds DNA and DNA is a double stranded molecule, not a single stranded oligonucleotide. Therefore, the DNA added in Ackley et al. is not the molecule of interest added in claim 13 element (b), nor does Ackley et al. suggest adding a molecule of interest to an oligonucleotide-containing microarray device. Accordingly, Ackley et al. does not anticipate the presently claimed invention nor does Ackley et al. suggest the presently claimed invention because of the addition of double stranded DNA.

With regard to Heller et al. (column 4 line 60 to column 5 line 17 and column 17 lines 38-45), this disclosure proves an electrode containing microarray device (similar to claim 13 element (a)) but made differently from the *in situ* electrochemistry process of Montgomery. Heller et al. is essentially a duplicate disclosure of Ackley et al. Specifically, the two sections cited by the Examiner refer to the "micro-locations" that are "addressed" to "direct the transport and attachment of specific binding entities." However, such micro-locations do not have oligonucleotide affinity anchor molecules as required in claim 13 element (a). Therefore, not only is Heller et al. not anticipatory of the entirety of claim 13, Heller et al. does not even anticipate only element (a) of claim 13. Moreover, Heller et al., does not suggest even element (a) of claim 13 and certainly does not suggest the remainder of claim 13. The same situation holds for process claim 17. Accordingly, Heller et al. does not anticipate the presently claimed invention nor do Heller et al. suggest the presently claimed invention because it does not disclose or suggest any of the elements of claims 13 or 17.

Finally, with regard to Hafeman et al. (column 3 line 27 to column 5 line 45) this disclosure does not disclose or suggest any portion of claims 13 or 17. Hafeman et al. relates to a photoresponsive electrode, a different animal from an electrochemistry system in the present invention. Accordingly, Hafeman et al. does not anticipate the presently claimed invention nor does Hafeman et al. suggest the presently claimed invention because of a different technology used for a different purpose that would not be operative in the inventive electrochemical system.

In summary, only Montgomery discloses claim 13 element (a) (and corresponding claim 17 step (a)) but does not disclose or suggest claim 13 element (b). None of the other references disclose or suggest claim 13 element (b) and its corresponding claim 17 steps. Therefore, none of the cited references individually anticipate the presently claimed invention. Further, none of the cited references individually suggest the presently claimed invention. Finally, as none of the cited references disclose or suggest claim 13 element (b) (and the corresponding process steps in claim 17), the combination of references, if they can be appropriately combined, do not collectively suggest the presently claimed invention.

Advisory Action Item 5

In the Advisory Action, item 5 is a response to the above argument (repeated above because the Amendment B was not entered. With regard to Montgomery, the Examiner alleged that the above argument was that Montgomery was "not **pertinent** to the claimed invention" (emphasis added) because "it is directed to an *in situ* electrochemical synthesis process to synthesize oligomers attached to an electrode and does not describe the instantly claimed hybridization of claim 17." Applicant respectfully disagrees with that characterization of the above argument. Claim 17 is not a hybridization of an oligonucleotide target to an electrode array. The difference is primarily in the molecule of interest. Claim 17 provides that the molecule of

interest have an oligonucleotide moiety **and a protein or antibody (or both) moiety**.

Montgomery, by contract, describes the electrode array and synthesizing an oligonucleotide within a porous matrix (Claim 17 element (a)). Once one looks at claim 17 element (b), there are patentable differences with Montgomery. In Montgomery, the hybridization reaction is with a piece of nucleic acid, in contrast with a molecule of interest (having an oligonucleotide moiety only and then addition parts). There is also a difference in element (c), wherein the antibody or protein or both moiety of the molecule of interest then is used for binding purposes. In Montgomery, the protein part (an antibody is a protein) does not exist so it cannot be used. Therefore the Examiner's assertion ("Montgomery also discloses the use of these immobilized oligonucleotides in convention hybridization") is incorrect because the binding reaction described in elements c-d (claim 17) is not a conventional hybridization but is a protein or antibody binding reaction. Therefore, once claim 17 is properly read it is apparent that Montgomery does not anticipate the process of claim 17 and that claim 17 is patentably distinct from Montgomery.

With regard to Hafeman et al., the Examiner has found relevant words in different parts of Hafeman but has not shown that the teachings of Hafeman describe an electrode array (note that an array needs many electrodes and not just an anode and cathode). Specifically, Hafeman describes a "photoresponsive electrode" and not an electrode. One skilled in the art will know that a photoresponsive electrode is not an electrode as that term is normally used in the art. Further, the photoresponsive electrode of Hafeman is not an electrode array device having a plurality of electrode cells as provided in claim 13 and illustrated (9 cells) in Figure 2. Instead, Hafeman has a single photoresponsive electrode (see Hafeman Summary section column 1 line 59 to column 2 line 3). Therefore, despite using words out of context, Hafeman does not disclose or suggest the claim 13 element (a) even with "film or coating" of column 4 line 41 and a sample to be tested in column 14. Moreover, no equivalent of claim 13 element (b) is disclosed or suggested in Hafeman.

Information Disclosure Statement

Applicant thanks the Examiner for considering the Information Disclosure Statement, as a copy of the signed off Form 1449 was included with the Advisory Action.

In view of the foregoing response, applicant respectfully requests withdrawal of the pending rejections, and allowance of pending claims 13, 15-17 and 19-20.

Respectfully submitted,

Jeffrey B. Oster
Attorney for Applicant
Registration No. 32,585

Combimatrix Corporation
6500 Harbour Heights Parkway
Mukilteo, WA 98275
Telephone (425) 493 2302
Facsimile (425) 493 2010

amdt. unsigned

Clean copy of pending claims:

13. A microarray device comprising:

(a) an electrode array device comprising a plurality of electrode cells, a porous matrix, and a plurality of affinity anchor molecules, wherein the affinity anchor molecule is an oligonucleotide, wherein the porous matrix overlays each electrode cell and wherein the plurality of affinity anchor molecules are located within the porous matrix; and

(b) a plurality of molecules of interest, wherein each molecule of interest comprises an oligonucleotide moiety that binds to a complementary affinity anchor molecule oligonucleotide and a binding entity selected from the group consisting of peptides, antibodies, and combinations thereof.

15. The microarray device of claim 13 wherein the electrode array comprises a plurality of electrode cells at a density of at least 100 electrodes per cm^2 .

16. The microarray device of claim 13 wherein the electrode array comprises a plurality of electrode cells at a density of at least 1000 electrodes per cm^2 .

17. A process for producing an array of molecules of interest localized to known locations, comprising:

(a) electrochemically synthesizing a plurality of different affinity anchor molecules at known locations within a porous matrix on an electrode microarray device, wherein the affinity anchor molecule is an oligonucleotides;

(b) providing a plurality of molecules of interest, wherein each molecule of interest comprises an oligonucleotide moiety that hybridizes to a complementary affinity anchor molecule and a binding entity selected from the group consisting of peptides, antibodies, and combinations thereof;

(c) contacting the plurality of molecules of interest with the microarray device, whereby the molecules of interest localize to known locations by binding the affinity anchor molecule to the complementary oligonucleotide moiety of the molecule of interest; and

(d) washing the microarray device to remove unbound molecules of interest.

19. The process of claim 17 wherein the electrode array comprises a plurality of electrode cells at a density of at least 100 electrodes per cm^2 .

20. The process of claim 17 wherein the electrode array comprises a plurality of electrode cells at a density of at least 1000 electrodes per cm^2 .